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| (54) Title: H ₂ ANTAGONIST-ANTIHISTAMINE COMBINATIONS | | | |
| (57) Abstract <p>This invention relates to pharmaceutical compositions for use in the prevention, treatment and relief of mild to moderate stomach and esophagus disorders such as indigestion, sour stomach, and heartburn while also treating symptoms associated with colds, flu and allergies, by administering compositions comprising (i) an amount effective in the relief of gastrointestinal or esophagus disorders of an H₂ antagonist selected from a compound of formula (I) and pharmaceutically acceptable salts, hydrates, stereoisomers or polymorphs thereof, and (ii) an antihistaminically effective amount of at least one of an antihistamine or a therapeutically active stereoisomer thereof substantially free of its other inactive or less active stereoisomers or a pharmaceutically acceptable salt, hydrate, or polymorph thereof, and optionally (iii) an anti-flamulent amount of a compound selected from simethicone, alpha-D-galactosidase, and a silicon based antiflatulent; with the proviso that NSAIDs or proton-pump inhibitors are not included.</p> <div style="text-align: center;"> <p>(I)</p> </div> | | | |

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TITLE OF THE INVENTIONH₂ ANTAGONIST-ANTIHISTAMINE COMBINATIONSBACKGROUND OF THE INVENTION

5 H₂ antagonists are commonly prescribed to treat and prevent ulcers in the walls of the stomach, duodenum or esophagus. H₂ antagonists are also used to treat non-ulcerative conditions. Damage to the mucus lining surrounding these tissues enables destructive action of stomach acids which erodes the underlying tissue. Commonly known
10 H₂ antagonists for the treatment of ulcers include cimetidine, ranitidine, nizatidine, roxatidine and famotidine.

Antihistamines useful for the treatment of cold, flu or allergy symptoms are generally categorized into conventional and non-sedating antihistamines. The conventional antihistamines exhibit an
15 anticholinergic effect which may be advantageous to the cold, flu or allergy sufferer. The conventional antihistamines may also have an advantage for the subject who wishes to induce drowsiness while concurrently relieving the targeted symptoms. Likewise, the non-conventional antihistamines have benefits to those patients in need of
20 treatment but who need to stay awake or alert. See *Martindale's The Extra Pharmacopoeia*, 443 (1989) and references cited therein. Antihistamines may also be useful in the treatment of nausea. Antihistamines are further classified into H₁ receptor antagonists and H₂ receptor antagonists and additionally are classified into five groups
25 based upon their chemical structure. These groups include the ethanolamines (e.g. diphenhydramine) which have both sedative effects and muscarinic effects; ethylenediamines (e.g. mepyramine) which apparently have less central activity but may produce skin sensitization and gastric disturbances; alkylamines (e.g. chlorpheniramine) which are
30 potent H₁ antagonists which have relatively little sedative effect and produce central nervous system stimulation; piperazines (e.g. meclizine) which have anti-emetic effects; and phenothiazines (e.g. promethazine) which have pronounced antimuscarinic effects, anti-emetic effects and cause sedation and photosensitivity reactions. Antihistamines have been

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utilized in a number of multiingredient formulations wherein diphenhydramine salts have been employed. Their primary use has been in combination cold, flu or allergy medications which also have analgesic properties. See *Martindale's The Extra Pharmacopoeia*, p. 453 (1989). Combinations of H₁ antagonists (including diphenhydramine) and H₂ antagonists and other active ingredients including NSAIDs or proton pump inhibitors have been disclosed. See U.S. Pat. Nos. 5,037,815 and 4,757,060; EPO 0 320 551 A1 and EPO 0 426 479 A1.

There is a need to employ a drug combination wherein an advantage is that the overall symptoms of gastrointestinal distress can be effectively treated with a combination of the most powerful H₂ antagonist available (famotidine) with an antihistamine wherein the combination simultaneously treats, relieves and prevents symptoms associated with excess gastric acid secretion or evolution in the stomach and esophagus respectively while also promoting flu, cold, allergy and/or nausea relief with a pharmaceutically effective amount of an antihistamine selected from the conventional or non-conventional antihistamines. This composition specifically excludes NSAIDs or proton pump inhibitors. The present invention therefore provides an effective dual treatment of gastrointestinal disorders using the combination of famotidine with an antihistamine such as diphenhydramine hydrochloride, and optionally and antifatulent. The claimed combination is particularly useful for treating gastrointestinal distress, including nausea, accompanied by cold, flu or allergy symptoms. The claimed combination is advantageously used at night since famotidine provides long lasting systemic relief while the diphenhydramine salt provides anti-cold, flu, allergy and nausea relief and has a sedative effect. Other H₂ antagonists that can be used with this invention include ranitidine, cimetidine, nizatidine and roxatidine.

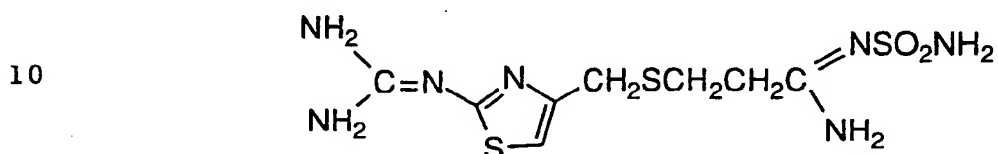
DETAILED DESCRIPTION OF THE INVENTION

This invention claims pharmaceutical compositions for use in the prevention, treatment and relief of mild to moderate stomach and

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esophagus disorders in patients in need of treatment thereof including the prevention, treatment and relief of heartburn while concomitantly treating symptoms associated with colds, flu, allergies and nausea. The composition comprises:

- 5 (i) an amount effective in the relief of gastrointestinal or esophagus disorders of an H₂ antagonist selected from a compound of the formula:



15 and pharmaceutically acceptable salts, hydrates, stereoisomers or polymorphs thereof thereof, and

- (ii) an antihistaminically effective amount of at least one of an antihistamine or a therapeutically active stereoisomer thereof substantially free of its other inactive or less active stereoisomers or a pharmaceutically acceptable salt, hydrate, or polymorph thereof, and optionally
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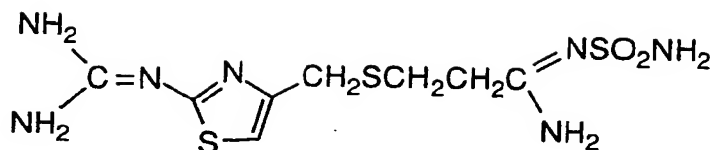
- (iii) an anti-flatulent amount of a compound selected from simethicone or alpha-D-galactosidase.
- 25

This invention is also directed to a method of preventing, relieving and treating indigestion, sour stomach, nausea, flatulence, heartburn, overindulgence, gastroesophageal reflux ("GER") and other gastrointestinal disorders and flu, cold and allergy symptoms in patients in need of treatment thereof, comprising administering to such organism:

30

- (i) an amount effective in the relief of gastrointestinal or esophagus disorders of an H₂ antagonist selected from a compound of the formula:

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5

and pharmaceutically acceptable salts, hydrates, stereoisomers or polymorphs thereof, and

- 10 (ii) an antihistaminically effective amount of at least one of an antihistamine or a therapeutically active stereoisomer thereof substantially free of its other inactive or less active stereoisomers or a pharmaceutically acceptable salt, hydrate, or polymorph thereof, and optionally

15

- (iii) an anti-flatulent amount of a compound selected from simethicone or alpha-D-galactosidase.

20 The terms mammals or mammalian organism or patients are used interchangeably herein, and include but are not limited to mammals such as humans, dogs, cats, horses and cows. The preferred patient in need of treatment thereof is a human.

25 The term treatment encompasses the complete range of therapeutically positive effects associated with pharmaceutical medication including reduction of, alleviation of and relief from the symptoms or illness which affect the organism.

30 Famotidine may be purchased in bulk quantities as it is currently available on the market, and formulated via typical formulation processes with antihistamines wherein the combination is suitable for tablet, capsule, effervescent, chewable tablet or liquid formulations of the claimed combination including known and effective delivery systems. Famotidine as a prescription drug product is sold in the United States under the trademark PEPCID®. The antihistamines claimed in combination with famotidine are available from numerous manufacturers. Simethicone is a well known anti-flatulent and is sold

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by a number of manufacturers. The quantities utilized to treat flatulence vary depending upon the severity of the condition. The Physicians Desk Reference, 46th Ed. (1992) on pages 1155-56 describes the various quantities and dosage regimes for typical simethicone
5 formulations. Alpha-D-galactosidase (ADG) is a known enzyme which degrades indigestible sugars found in beans or bean products. These anti-flatulents may be added as optional ingredients to the H₂ antagonist/antihistamine combination. The active ingredients in the claimed combination are therefore readily available. See also European
10 Patent Application 0,076,530 published on April 13, 1983.

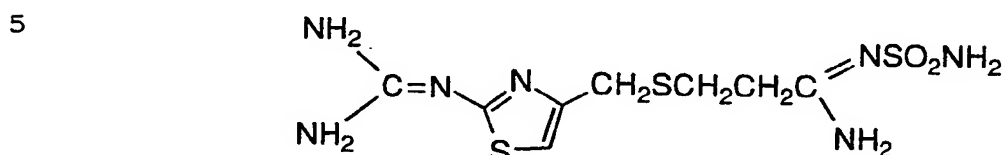
Where only a single stereoisomer of the antihistamine is active as the therapeutically active stereoisomer, the absence of the inactive stereoisomer of the antihistamine in the present composition avoids undesirable side effects that may accompany ingestion and
15 metabolism of the non-biologically active stereoisomer. These include any toxic interactions and in addition metabolic energy is saved when only one stereoisomer of the antihistamine is used in the claimed combination. The use of the potent H₂ antagonist such as famotidine combined with an antihistamine or an active stereoisomer of an
20 antihistamine provides significant dosage form advantages since less of the H₂ antagonist and the antihistamine is needed to formulate a suitable dosage form and provides for a more practical size tablet or capsule.

The pharmaceutical compositions of the present invention are useful in the prevention, treatment and relief of various mild to
25 moderate gastrointestinal disorders including indigestion, sour stomach, overindulgence, heartburn, gastroesophageal reflux, nausea, and flatulence if an optional anti-flatulent is added. The compositions are also useful in the treatment of symptoms such as runny nose, sneezing, sniffles and itchy or watery eyes that often accompany colds, flus or
30 allergies.

In particular, an antihistamine selected from either the conventional or non-conventional class, or further selected from an H₁ receptor antagonist or an H₂ receptor antagonist and in particular from members of the five known chemical classes, including but not limited

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to the biologically active and pharmaceutically effective stereoisomers thereof in substantially pure form, combined with an H₂ antagonist selected from famotidine, a compound of the formula:



10 or its pharmaceutically acceptable salts, hydrates, stereoisomers or polymorphs thereof, is useful for the prevention and treatment of various gastrointestinal disorders such as indigestion, sour stomach, or heartburn or other disorders as described herein, and cold, allergy and flu symptoms as well as nausea. The utilization of the currently known
15 biologically active forms and/or salts or hydrates of famotidine in combination with an antihistamine or other pharmaceutically acceptable antihistamine salt or hydrate is advantageously used to prevent, relieve and treat mild to moderate gastrointestinal disorders and cold, flu and allergy symptoms. Furthermore, with the addition of simethicone or
20 ADG, the composition is also advantageously used to provide anti-flatulent relief. In particular, the claimed combination is used to prevent, treat and relieve the symptoms associated with gastric acid secretion while simultaneously preventing, relieving and treating the symptoms of gastro-esophageal reflux and colds, flu and allergy, and
25 optionally, flatulence. Therefore, the animal, patient, or organism in need of treatment thereof benefits from the claimed pharmaceutical composition.

H₂ antagonists are well known in the treatment of ulcers and other gastrointestinal disorders and may be used, according to the
30 present invention, in combination with an antihistamine and optionally with the addition of simethicone or ADG. H₂ antagonists used for ulcer therapy fall into four major structural classes: imidazole derivatives; substituted furans; aminoalkylphenoxy derivatives and guanidinothiazole compounds. Famotidine (N'-(aminosulfonyl)-3-[[[2-[(diamino-methylene)amino]-4-thiazolyl]methyl]thio] propanimidamide), a

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member of the last-noted class above, is a competitive inhibitor of histamine H₂-receptors and its primary pharmacological activity is the inhibition of gastric acid secretion. Famotidine suppresses both the acid concentration and the volume of gastric acid secretion. Famotidine is well tolerated and has minimal side effects and thus advantageously may be used in the present invention in combination with an antihistamine. Famotidine is also the most potent and selective H₂ antagonist.

Antihistamines are used to diminish or alleviate the actions of histamine in mammalian organisms by competitive or reversible blockade of histamine receptor sites on mammalian tissues. Antihistamines are also useful for the treatment of nausea. H₁ receptors when activated cause vasodilation, increased capillary permeability, flare and itch reactions of the skin and contraction of smooth muscle in the bronchi and gastrointestinal tract while H₂ receptors when activated promote gastric acid secretion and vasodilation. H₁ antagonists are useful to treat allergic reactions while antihistamines are generally effective in relieving symptoms of seasonal rhinitis, perennial allergic rhinitis and various other disorders as listed and described in *Martindale's The Extra Pharmacopoeia*, (1989) on page 444. In a preferred embodiment, diphenhydramine hydrochloride, also known as 2-benzhydryloxy-N,N-dimethylethylamine hydrochloride, is used as the antihistamine in the present invention in combination with famotidine. Antihistamines may also be used to alleviate nausea.

The antihistamines employed herein are selected from the conventional or non-sedating types and may further be chosen from the five distinct chemical classes. The conventional antihistamines competitively antagonize those pharmacological effects of histamine which are mediated through activation of histamine H₂ receptor sites on effector cells. The conventional antihistamines also exhibit an anticholinergic (drying) effect. The conventional antihistamine is selected from, for example, chlorpheniramine, brompheniramine, dexchlorpheniramine, dexbrompheniramine, tripeleminamine, cypheptadine, carbinoxamine, bromodiphenhydramine,

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diphenhydramine or a pharmaceutically acceptable salt, hydrate, or polymorph thereof.

5 The non-sedating antihistamine is selected from, for example, acirvastine, AHR-11325, astemizole, azelastine, cetirizine, ebastine, ketotifen, lodoxamide, loratidine, levocabastine, mequitazine, oxatomide, setastine, tazifylline, temelastine or terfenadine or a pharmaceutically acceptable salt, hydrate, or polymorph thereof.

10 Included within this invention are any diastereomers and/or enantiomers of each antihistamine. In particular, a therapeutically active stereoisomer of an antihistamine, such as diphenhydramine HCL, substantially free of its other inactive or less active stereoisomers may be employed in the instant invention. As used herein, the phrase "a therapeutically active stereoisomer substantially free of its other inactive or less active stereoisomers" means that the ratio of active stereoisomer to inactive or less active stereoisomer(s) is at least 90:10. Where a particular therapeutically active stereoisomer is not commercially available it may readily be prepared following standard resolution chemistry or purification technology known in the art. For example, high performance liquid chromatography ("HPLC") or other suitable chromatographic or separation means may be used to purify or isolate the active stereoisomer (enantiomer or diastereomer) from its readily available racemic mixture.

25 The combination of famotidine or its pharmaceutically effective salts, hydrates, stereoisomers or polymorphs thereof with an antihistamine and an optional anti-flatulent provides a combination which simultaneously and selectively provides prevention, treatment and relief of discomfort and injury to the stomach, esophagus, or duodenum from excess production of gastric acid while concurrently treating cold, allergy and flu symptoms and optionally flatulence. Furthermore, famotidine in combination with an antihistamine may not interact with alcohol so that it may be administered prior to or during ingestion of meals or beverages which contain alcohol and, therefore, a patient in need of rapid treatment of gastrointestinal distress may take the drug combination at an appropriate time which may be during a meal in

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which alcohol was consumed. The combination of an antihistamine with famotidine provides relief of gastroesophageal reflux while also providing long acting relief from and treatment of gastrointestinal disorders associated with gastric acid secretion.

5 The combination of famotidine which is a highly potent H₂ antagonist with an antihistamine and optionally with an antifatulent, reduces the size and weight of all pharmaceutical delivery forms or combination formulations and therefore improves patient compliance or tolerance. The tablet or capsule form of this combination is more
10 readily swallowable by patients in need of treatment thereof.

 Famotidine, or a pharmaceutically effective salt, hydrate, stereoisomer or polymorph thereof, is advantageously used in the present invention in combination with an antihistamine, for example one
15 selected from the ethanolamine class such as diphenhydramine hydrochloride, and optionally with an antifatulent. The amount of antihistamine added per dosage may be from 1-200 mgs depending upon the specific drug. The amount of famotidine used in the present
invention in humans may range from 2.5 mg/dosage to 80mg/dosage . Advantageously, 5 to 40 mgs/dosage is administered in combination
20 with 10 to 50 mgs/dosage of diphenhydramine hydrochloride. For example, a tablet containing 5 mgs of famotidine may be administered 4 times daily with an effective amount of diphenhydramine and suitable inert ingredients also contained within the tablet.

 When employed, the amount of simethicone per dosage
25 may vary depending upon the degree of antifatulent strength desired, and may range, e.g., from 20 to 80 mgs. Maximum strength antifatulents administered in tablet form four times per day may contain 125 mgs of simethicone per tablet. Currently marketed and available antacid/anti-
gas formulations contain, for example, 20-40 mgs/chewable tablet or
30 teaspoonful of liquid suspension of simethicone and 200 mgs of aluminum hydroxide and 200 mgs of magnesium hydroxide. Two to four tablets between meals or at bedtime or 2-4 teaspoonfuls between meals and at bedtime containing the above quantities are administered daily. ADG is an enzyme known to assist in the hydrolysis of

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indigestible sugars which are often found in beans or bean products. The quantity of ADG utilized in the present invention depends upon the concentration of active enzyme and upon the quantity of beans or other source of indigestible sugars ingested. Generally, the amount of ADG
5 that may be employed ranges from about 675 to 31,000 GalU ("alpha galactosidase units"), and preferably from about 675 to 2250 GalU. See WO90/14101 or PCT/US90/02643.

The quantities of each of the active ingredients may vary depending upon the severity of the condition and the particular
10 biochemistry and need of the patient or other organism in need of treatment thereof. The quantities of the active ingredient may also vary depending upon whether the active ingredients are administered in tablet or liquid form or via some other suitable delivery method. A physician
15 or clinician or veterinarian of ordinary skill in the art may readily determine suitable dosages of any prescription medication containing the claimed invention. The combination claimed in the instant invention is advantageously administered orally. However, in patients with hypersecretory conditions, intractable ulcers, or in patients who are
20 unable to take oral medication, the claimed combination may be administered intravenously in a suitable dosage within the limits described for oral treatment if the optional simethicone is not included.

The present composition may be administered in the form of tablets, caplets, gelcaps, capsules, elixirs, syrups, effervescent,
25 lozenges, fast-dissolving wafers or suspensions. For oral administration, the active ingredients may be admixed with a pharmaceutically acceptable diluent such as lactose, sucrose, cellulose, dicalcium phosphate, calcium sulfate, mannitol, and, in a liquid composition, ethyl alcohol. Acceptable emulsifying or suspending
30 agents such as PVP, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium an antihistamine, guar gum, agar, bentonite, carboxymethylcellulose sodium, polyethylene glycol and waxes, may also be admixed with the active components. Where necessary, lubricants such as magnesium stearic acid talc or magnesium stearate, and disintegrators or superdisintegrators such as starch,

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sodium starch glycolate or cross-linked PVP may also be included. Electrolytes such as dicalcium phosphate, sodium benzoate, sodium acetate and sodium chloride may also be used.

5 The active components may also be formulated in sustained release or effervescent formulations. These formulations depending upon whether they are sustained release or effervescent may be employed in oral, dermal, rectal or vaginal administrations. The sustained release formulations also include layered formulations which provide for distinct release ratio and thus may be more effective in
10 allowing for short and long term relief.

The following examples illustrate the compositions of the present invention which may be readily prepared and as such are not to be considered as limiting the invention set forth in the claims.

15

EXAMPLE 1

an antihistamine/famotidine Tablet

| | | |
|----|---------------------|-------|
| 20 | diphenhydramine HCl | 50 mg |
| | famotidine | 40 mg |
| | PVP | 15 mg |
| | Avicel PH101 | 40 mg |
| | Magnesium Stearate | 4 mg |

25

EXAMPLE 2

an antihistamine/famotidine Tablet

| | | |
|----|---------------------|-------|
| 30 | diphenhydramine HCl | 40 mg |
| | famotidine | 20 mg |
| | PVP | 15 mg |
| | Avicel PH101 | 40 mg |
| | Magnesium Stearate | 4 mg |

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EXAMPLE 3

| | | |
|---|------------------------------------|-------|
| | an antihistamine/famotidine Tablet | |
| 5 | diphenhydramine HCl | 20 mg |
| | famotidine | 15 mg |
| | PVP | 15 mg |
| | Avicel PH101 | 40 mg |
| | Magnesium Stearate | 4 mg |

10

EXAMPLE 4

| | | |
|----|---|---------|
| | <u>an antihistamine/famotidine Tablet</u> | |
| 15 | diphenhydramine HCl | 12.5 mg |
| | famotidine | 10 mg |
| | PVP | 15 mg |
| | Avicel PH101 | 40 mg |
| | Magnesium Stearate | 4 mg |

20

EXAMPLE 5

| | | |
|----|---|---------|
| | <u>an antihistamine/famotidine Tablet</u> | |
| 25 | diphenhydramine HCl | 12.5 mg |
| | famotidine | 5 mg |
| | PVP | 15 mg |
| | Avicel PH101 | 40 mg |
| | Magnesium Stearate | 4 mg |

30

EXAMPLE 6an antihistamine/famotidine Sustained Release

| | | |
|--|---------------------|-------|
| | diphenhydramine HCl | 50 mg |
| | famotidine | 40 mg |

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| | | |
|---|--------------------|--------|
| | PVP | 30 mg |
| | Avicel PH101 | 80 mg |
| | Magnesium Stearate | 8 mg |
| | Methocel E10MCR | 66 mg |
| 5 | Methocel K100MLV | 200 mg |

EXAMPLE 7an antihistamine/famotidine Sustained Release

| | | |
|----|---------------------|--------|
| 10 | diphenhydramine HCl | 50 mg |
| | famotidine | 20 mg |
| | PVP | 30 mg |
| | Avicel PH101 | 80 mg |
| 15 | Magnesium Stearate | 8 mg |
| | Methocel E10MCR | 66 mg |
| | Methocel K100MLV | 200 mg |

EXAMPLE 8an antihistamine/famotidine Solution

| | | |
|----|---------------------|---------|
| 20 | diphenhydramine HCl | 12.5 mg |
| | famotidine | 10 mg |
| 25 | g.s. syrup | 5 ml |

EXAMPLE 9an antihistamine/famotidine Solution

| | | |
|----|---------------------|-------|
| 30 | diphenhydramine HCl | 50 mg |
| | famotidine | 20 mg |
| | g.s. syrup | 5 ml |

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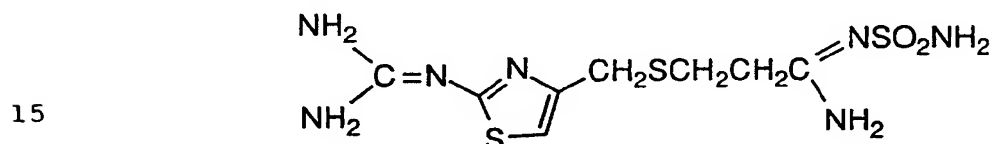
Simethicone or alpha-D-galactosidase may be added to each of the above formulations or examples to provide anti-flatulent relief. The quantity of simethicone administered to a patient in need of treatment thereof may vary according to patient need, but may be, for example, the typical known dosage range to treat flatulence (20-40 mgs per tablet or per 5 ml liquid dosage form) or may be increased as necessary. Generally, the amount of ADG that may be employed in the above formulations ranges from about 675 to about 2250 GalU, or may be increased as necessary. The inactive ingredients in the tablet form may further include dextrates, mannitol, magnesium stearate, Yellow 10, colloidal silicon dioxide and Blue 1 or Red 27 while the liquid form(s) may further include inactives such as butylparaben, carboxymethylcellulose sodium, flavors, hydroxypropyl methylcellulose, microcrystalline cellulose, propylparaben, and purified water. The previous examples are to be construed as non-limiting and additional dosages and dosage forms or routes of administration may be varied depending upon the individual patient being treated for either the primary (excess acid leading to gastrointestinal or esophageal disturbance or damage) or secondary (infections) symptoms of gastrointestinal disorders. In addition, known pharmaceutically acceptable excipients or agents may be added as inactive ingredients to the claimed active combination in a variety of forms including tablets, capsules, or time-release medicaments.

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WHAT IS CLAIMED IS:

1. A pharmaceutical composition for use in the prevention, treatment and relief of gastrointestinal disorders such as indigestion, sour stomach, overindulgence, gastroesophageal reflux, nausea and heartburn and cold, flu and allergy symptoms in a patient in need of treatment thereof, comprising:

(i) an amount effective in the relief of gastrointestinal or esophagus disorders of an H₂ antagonist selected from a compound of the formula:



and pharmaceutically acceptable salts, hydrates, stereoisomers or polymorphs thereof, and

(ii) an antihistaminically effective amount of at least one of an antihistamine or a therapeutically active stereoisomer thereof substantially free of its other inactive or less active stereoisomers or a pharmaceutically acceptable salt, hydrate, or polymorph thereof, and optionally

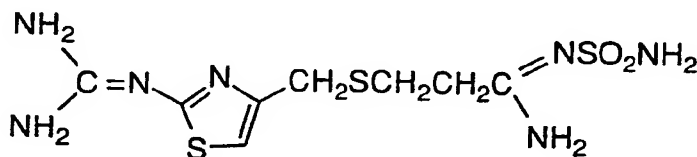
(iii) an antifatulent effective amount of an antifatulent; with the proviso that the composition excludes NSAIDs or proton pump inhibitors.

2. The pharmaceutical composition according to Claim 1 for use in the prevention, treatment and relief of gastrointestinal disorders such as indigestion, sour stomach, overindulgence, gastro-

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esophageal reflux, nausea and heartburn and cold, flu and allergy symptoms in a patient in need of treatment thereof, comprising:

- (i) an amount effective in the relief of gastrointestinal or esophagus disorders of an H₂ antagonist selected from a compound of the formula:



and pharmaceutically acceptable salts, hydrates, stereoisomers or polymorphs thereof, and

- (ii) an antihistaminically effective amount of at least one of an antihistamine or a therapeutically active stereoisomer thereof substantially free of its other inactive or less active stereoisomers or a pharmaceutically acceptable salt, hydrate, or polymorph thereof, wherein the antihistamine is selected from a conventional antihistamine or a non-sedating antihistamine, and optionally
- (iii) an antifatulent effective amount of an antifatulent selected from simethicone, a silicon based antifatulent, and alpha-D-galactosidase.
3. The composition of Claim 2 comprising
- (i) from 2.5 mgs to 80 mgs of famotidine or a pharmaceutically acceptable salt, hydrate, stereoisomer or polymorph thereof, and
- (ii) from 1 mg to 200 mgs of an anti-histamine, and optionally

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(iii) from 20 mgs to 125 mgs of simethicone or 675 -
31,000 GalU of alpha-D-galactosidase,
wherein the conventional antihistamine is selected from chlorphenir-
amine, brompheniramine, dexchlorpheniramine, dexbrompheniramine,
5 triprolidine, doxylamine, tripeleminamine, cyproheptadine, carbinox-
amine, bromodiphenhydramine, phenidamine, pyrilamine, azatadine,
diphenhydramine, and the non-sedating antihistamine is selected from
acrivastine, AHR-11325, astemizole, azelastine, cetirizine, ebastine,
10 ketoifen, lodoxamine, loratidine, levocabastine, mequitazine, oxatomide,
setastine, tazifylline, temelastine or terfenadine, or a therapeutically
active stereoisomer of any of the above-named compounds substantially
free of its other inactive or less active stereoisomers or a
pharmaceutically acceptable salt, hydrate, or polymorph thereof.

15 4. The composition according to Claim 3 comprising
(i) from 5 to 40 mgs of famotidine or a
pharmaceutically acceptable salt, hydrate,
stereoisomer or polymorph thereof, and
20 (ii) from 10 to 50 mgs of diphenhydramine HCl, and
optionally
(iii) from 20 mgs to 80 mgs of simethicone or 675 to
25 2250 GalU of alpha-D-galactosidase.

5. The composition according to Claim 4 wherein the
optional amount of simethicone is from 20 mgs to 40 mgs.

30 6. A pharmaceutical composition comprising a
pharmaceutically effective amount of:
(i) famotidine or a pharmaceutically acceptable salt,
hydrate, stereoisomer or polymorph thereof;

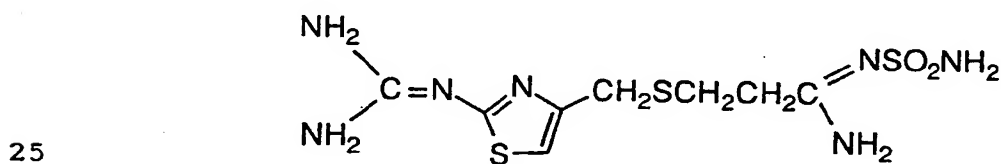
- 18 -

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- (ii) diphenhydramine HCl or a pharmaceutically acceptable hydrate, stereoisomer or polymorph thereof;
- (iii) a pharmaceutically acceptable excipient; and optionally
- (iv) an antifatulent selected from simethicone, alpha-D-galactosidase, and a silicon based antifatulent;
- 10 wherein the composition excludes NSAIDs or proton pump inhibitors.

7. A method of preventing, relieving and treating gastrointestinal disorders such as indigestion, sour stomach, over-indulgence, gastroesophageal reflux, heartburn, nausea and cold, flu and allergy symptoms in a mammalian organism in need of such treatment, comprising administering to such organism:

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- (i) an amount effective in the relief of gastrointestinal or esophagus disorders of an H₂ antagonist selected from a compound of the formula:
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and pharmaceutically acceptable salts, hydrates, stereoisomers or polymorphs thereof, and

- 30
- (ii) an antihistaminically effective amount of at least one of an antihistamine or a therapeutically active stereoisomer thereof substantially free of its other inactive or less active stereoisomers or a pharmaceutically acceptable salt, hydrate, or polymorph thereof, and optionally

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(iii) an antifatulent effective amount of an antifatulent; with the proviso that the composition excludes NSAIDs or proton pump inhibitors.

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8. The method according to Claim 7 wherein the composition administered to a mammalian organism in need thereof comprises:

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(i) famotidine or a pharmaceutically acceptable salt, hydrate, stereoisomer or polymorph thereof; and

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(ii) diphenhydramine HCl or a pharmaceutically acceptable hydrate, stereoisomer or polymorph thereof; and optionally

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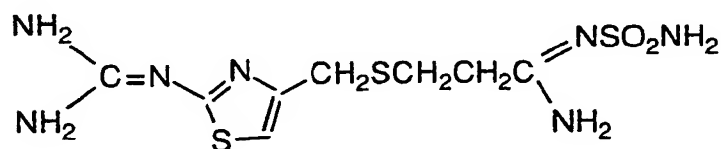
(iii) an antifatulent effective amount of a compound selected from simethicone, a silicon based antifatulent and alpha-D-galactosidase.

9. A method of reducing the size and weight of a pharmaceutically effective amount of an antihistamine/H₂ antagonist combination dosage form which comprises combining

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(i) an amount effective in the relief of gastrointestinal or esophagus disorders of an H₂ antagonist selected from a compound of the formula:

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and pharmaceutically acceptable salts, hydrates, stereoisomers or polymorphs thereof, and

(ii) an antihistaminically effective amount of at least one of an antihistamine or a therapeutically active stereo-

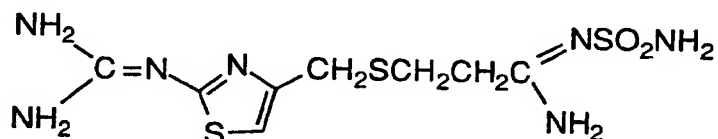
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isomer thereof substantially free of its other inactive or less active stereoisomers or a pharmaceutically acceptable salt, hydrate, or polymorph thereof, and optionally

- (iii) an antifatulent effective amount of a compound selected from simethicone, a silicon based antifatulent and alpha-D-galactosidase.

10. A method of treating gastrointestinal disorders, over-indulgence and pain before or during ingestion of a meal accompanied by alcoholic beverages, comprising: administration of a combination of

- (i) an amount effective in the relief of gastrointestinal or esophagus disorders of an H₂ antagonist selected from a compound of the formula:



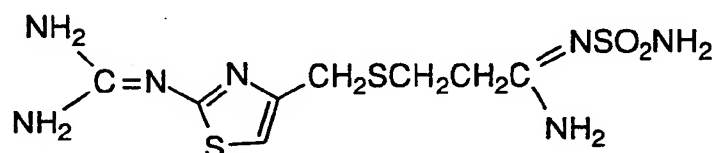
and pharmaceutically acceptable salts, hydrates, stereoisomers or polymorphs thereof wherein the famotidine does not interact with ethanol from the ingestion of the alcoholic beverage, and

- (ii) an antihistaminically effective amount of at least one of an antihistamine or a therapeutically active stereoisomer thereof substantially free of its other inactive or less active stereoisomers or a pharmaceutically acceptable salt, hydrate, or polymorph thereof, and optionally
- (iii) an antifatulent effective amount of a compound selected from simethicone, a silicon based antifatulent, and alpha-D-galactosidase.

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11. A method of treating gastrointestinal disorders, overindulgence and pain at bedtime, comprising: administration of a combination of

- 5 (i) an amount effective in the relief of gastrointestinal or esophagus disorders of an H₂ antagonist selected from a compound of the formula:



and pharmaceutically acceptable salts, hydrates, stereoisomers or polymorphs thereof, and

- 15 (ii) an antihistaminically effective amount of at least one of an antihistamine or a therapeutically active stereoisomer thereof substantially free of its other inactive or less active stereoisomers or a pharmaceutically acceptable salt, hydrate, or polymorph thereof, and optionally
- 20 (iii) an antifatulent effective amount of a compound selected from simethicone, a silicon based antifatulent and alpha-D-galactosidase.
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US94/07528

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : A61K 31/425; A01N 43/78; C07D 277/04, 277/60

US CL : 424/94.4; 514/365, 370, 371; 548/146, 190, 200

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/94.4; 514/365, 370, 371; 548/146, 190, 200

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
THE MERCK INDEXElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Extra Sheet.**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---------------|---|-----------------------------|
| X --- Y | DRUGS, Volume 38, Number 4, issued 1989, Advenier et al, "Rational Use of Antihistamines in Allergic Dermatological Conditions", pages 634-644, see especially pages 638, 639 and 641. | 1, 2, 6 ----- 3, 4, 5 |
| X -- Y | RESEARCH COMMUNICATIONS IN CHEMICAL PATHOLOGY AND PHARMACOLOGY, Volume 79, Number 2, issued February 1993, S. Kaneta et al, "Effects of H2-Antihistamines in Murine Models of Immediate Hypersensitivity and Chronic Inflammation", pages 167-184, especially page 170. | 1, 2, 6 ----- 3, 4, 5 |

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

| | | |
|---|-------|--|
| * Special categories of cited documents: | *T | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| *A* document defining the general state of the art which is not considered to be of particular relevance | *X* | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| *E* earlier document published on or after the international filing date | *Y* | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | * & * | document member of the same patent family |
| *O* document referring to an oral disclosure, use, exhibition or other means | | |
| *P* document published prior to the international filing date but later than the priority date claimed | | |

Date of the actual completion of the international search

27 SEPTEMBER 1994

Date of mailing of the international search report

17 OCT 1994

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/07528

| C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|---|---|-----------------------------|
| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X -- Y | MOLECULAR PHARMACOLOGY, Volume 42, issued August 1992, R. Seifert et al, "Histamine Increases Cytosolic Ca ²⁺ in HL-60 Promyelocytes Predominantly via H ₂ Receptors with an Unique Agonist/Antagonist Profile and Induces Functional Differentiation", pages 235-241, especially page 235. | 1, 2, 6 ----- 3, 4, 5 |
| Y | VRACH DELO, Number 8, issued August 1990, G.V. Leont'eva et al, "A Morphometric Analysis of Tissue Homeostasis in Peptic Ulcer Patients during Treatment with Antihistamine Preparations", pages 39-41, see abstract. | 1-11 |
| Y | DIGESTIVE DISEASES AND SCIENCES, Volume 26, Number 4, issued April 1981, C. H. Cho et al, "Gastrointestinal Ulceration in the Guinea Pig in Response to Dimaprit, Histamine and H ₁ - and H ₂ - Blocking Agents", pages 306-311, see abstract. | 1-11 |
| Y | S. BUDAVERI et al, "THE MERCK INDEX" published 1989 by Merck & Co., Inc. (Rahway, N.J.), page 617, see second column, entry number 3881. | 1-11 |
| Y | WO, A, 92/00102 (DAVIS ET AL) 09 January 1992, see entire document. | 1-11 |
| Y | EP, A, 0,320,551 (PIALA ET AL) 21 June 1987, see entire document. | 1-11 |

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/07528

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS, CAS ONLINE, MEDLINE, REGISTRY, EMBASE, BIOSIS

search terms: ulcer or anti-ulcer?, (H1 or H2) and (receptor or blocker or antihistamine), diphenhydramine, famotidine, antifatulent or antacid